

Remarks

Reconsideration of this Application is respectfully requested.

I. Status Of The Claims, Support For The Amendment, And Request For Rejoinder

Claims 1-120 are pending.

Applicants propose to amend claims 25, 26, 47, 51, 57 and 166. The proposed amendments are intended to be made without prejudice or disclaimer.

The claims in this application were restricted by the Examiner. In response to Applicants' election of group I and the species election, the Examiner indicated at page 2 of the Office Action mailed July 25, 2006 that claims 27, 66, 71, 79, 80, 96, 97, 104 and 106-109 are withdrawn from consideration. Applicants request that these claims be rejoined following allowance of a generic claim.

II. The Examiner Interview

The undersigned met with the Examiner on April 10, 2007, to discuss the present application. During the interview, the undersigned and the Examiner discussed the outstanding enablement rejection. It is the undersigned's understanding that the Examiner would consider claims that recite "treating thrombosis." In a followup telephone conversation with the Examiner on April 12, 2007, the undersigned and the Examiner briefly discussed whether the proposed "treating thrombosis, or obtaining an

anti-thrombogenic effect" language, *e.g.*, in claim 25, would be acceptable. The undersigned thanks the Examiner for the followup telephone conversation.¹

During the interview on April 10, 2007, the undersigned and the Examiner also discussed the outstanding obviousness rejection over Claeson (*Biochem J.*, 1993) in view of Skordalakes (*J. Am. Chem. Soc.*, 1997), and further in view of Kettner (WO 94/21668), Wienand (WO 97/05161) and/or Shoichet (WO 00/35904). The Examiner explained that he would consider further arguments and evidence, *e.g.*, in the form of the stability report (attached to the non-entered amendment filed April 19, 2007), in support of the nonobviousness of the claimed invention.

The undersigned and the Examiner also discussed the outstanding obviousness-type double patenting rejections. The undersigned requested that the rejections over copending Application Nos. 10/937,181 and 10/937,854 be withdrawn, as these applications were filed after the present application and remain pending.

Applicants and the undersigned thank the Examiner for the courteous and frank discussion of outstanding rejections.

III. The Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 25-26, 47-57, 112-113 and 116 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Applicants respectfully traverse this rejection.

The has Examiner acknowledged that the specification enables methods of "reducing thrombin," "treating thrombosis" and "treating deep vein thrombosis and/or pulmonary embolism." Office Action at page 3. However, the Examiner asserted that

¹ In the non-entered amendment filed April 19, 2007 Applicants proposed to amend certain claims to recite "obtaining an antithrombogenic effect." However, in the

the specification "does not reasonably provide enablement for inhibiting thrombin in the treatment [or] prevention of diseases or preventing thrombosis, cardiovascular event, venous thromboembolic event, thromboembolic events or arterial diseases." *Id.* Applicants respectfully disagree with this assertion, for at least the following reasons.

A. The Standard Establishing A Prima Facie Case Of Non-Enablement

The initial burden of proving that a specification is non-enabling is on the Examiner. Under controlling Federal Circuit case law, it is axiomatic that a specification is presumed to be enabling unless the Examiner provides acceptable objective evidence or sound scientific reasoning showing that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. In *In re Cortright*, 165 F.3d 1353 (Fed. Cir. 1999), the court stated that the PTO cannot make a section 112, first paragraph, rejection for lack of enablement, unless the PTO "has reason to doubt the objective truth of the statements contained in the written description." See 165 F.3d at 1357. The *Cortright* panel cited *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In *Marzocchi*, the court stated:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

439 F.2d at 223.

Advisory Action, the Examiner explained that this language would not be acceptable.

Thus, under *Cortright* and *Marzocchi*, the claims in an application are presumed to be enabled, unless proven otherwise. Further, it is well-established that some experimentation is permitted, so long as it is not "undue." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation.") (footnotes omitted); *see also Ex parte Forman*, 230 USPQ2d 546, 547 (BPAI 1986) ("The ultimate question . . . is whether or not the specification contains a sufficiently explicit disclosure to enable one having ordinary skill in the relevant field to practice the invention claimed therein without the exercise of undue experimentation.").

Here, the Examiner has failed to provide acceptable objective evidence or sound scientific reasoning showing that it would have required undue experimentation for one of ordinary skill in the art to practice the "prevention" methods of *properly interpreted* claims 25, 26, 47-57, 112, 113 and 116.

B. The Rejection Turns On An Incorrect Interpretation Of What "Preventing" Means

1. The Examiner Has Interpreted "Preventing" Overbroadly

The Examiner cited *The American Heritage Dictionary* for the definition of "prevent" as "to keep from happening; to keep from doing something," and asserted that "[t]he interpretation of the instant claims allows for the prevention, *cure, eradication or total elimination of* thrombosis or any diseases or conditions associated with thrombosis by the administration of said compounds." Office Action at page 4 (emphasis added).

Building upon this definition, the Examiner stated that “[t]here are no known compounds of similar structure which have been demonstrated to prevent thrombosis or treatment of any disease or condition related to thrombosis,” that “this assertion is contrary to what is known in medicine,” and that “[t]he existence of such a ‘magic bullet’ is contrary to our present understanding of pharmacology.” Office Action at pages 4-5. Applicants respectfully disagree.

The Examiner's use of a general purpose dictionary to interpret the claims of the present application is at odds with the claim interpretation standard established by the MPEP and the Federal Circuit's directive in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). It is true that “[d]uring patent examination, the pending claims must be ‘given their broadest *reasonable* interpretation consistent with the specification.’” MPEP § 2111 (emphasis added). “The Federal Circuit has expressly recognized that the USPTO employs the ‘broadest *reasonable* interpretation’ standard[.]” *Id* (emphasis added).

However, what is “reasonable” is determined through the lens of what one of ordinary skill in the art would understand. As the MPEP explains,

The Patent and Trademark Office (“PTO”) determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction “in light of the specification *as it would be interpreted by one of ordinary skill in the art.*”

MPEP § 2111 (emphasis added) (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (*en banc*). As further provided in MPEP § 2111, “[t]he broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach.”

Here, the Examiner has interpreted the claim term “preventing” incorrectly, because the Examiner’s interpretation is contrary with how one of ordinary skill in the art would have interpreted the term “preventing” in the context of clinical therapy for thrombosis. Thus, contrary to the Examiner’s interpretation of “preventing” to mean “cure, eradication or total elimination of thrombosis,” the term “preventing” would have been understood to mean “prophylaxis” and “reduction of risk.”

The Examiner’s overly broad interpretation of the term “preventing” is similar to the facts in *Cortright*. In *Cortright*, the claims related to a method of treating scalp baldness with an antimicrobial to *restore* hair growth.” 165 F.3d at 1355 (emphasis added). As explained in the MPEP,

The Board’s construction of the claim limitation “*restore hair growth*” as requiring the hair to be returned to its original state was held to be an incorrect interpretation of the limitation. The court held that, consistent with applicant’s disclosure and the disclosure of three patents from analogous arts using the same phrase to require *only some increase* in hair growth, one of ordinary skill would construe “*restore hair growth*” to mean that the claimed method increases the amount of hair grown on the scalp, but does not necessarily produce a full head of hair.

MPEP § 2111 (emphasis added) (citing *Cortright*, 165 F.3d at 1359). Thus, in *Cortright*, the term “*restore*” was interpreted to mean “*increase*,” not “*return to its original state*.”

C. “Preventing” Means “Prophylaxis” And “Reduction Of Risk”

Here, the term “*prevent*” is analogous to the term “*restore*” in *Cortright*. Analogously with *Cortright*, the recitation of the term “*preventing*” in the present claims

should be interpreted to mean “prophylaxis,” not “cure, eradication or total elimination of thrombosis.”

Evidence that one of ordinary skill in the art would have interpreted the term “prevent” to mean “prophylaxis” is found in the clinical literature. For example, in J.A. Heit, “The Potential Role of Direct Thrombin Inhibitors in the Prevention and Treatment of Venous Thromboembolism,” *CHEST*, 2003, 124, 40S-48S (“Heit”; copy attached to the non-entered amendment filed April 19, 2007):

Venous thromboembolism (VTE) is a common and potentially lethal disease that recurs frequently and is associated with long-term impairment and suffering. . . . [U]niversal effective prophylaxis of hospitalized patients would significantly *reduce the incidence of* VTE. Parenteral direct thrombin inhibitors are safe and effective for both *prevention* and treatment of acute VTE

Heit, at 40S, abstract (emphasis added). Thus, a person of ordinary skill in the art would have understood prevention or prophylaxis of a disorder to mean “reducing the incidence of” the disorder.

Similarly, W.H. Geerts *et al.*, “Prevention of Venous Thromboembolism,” *CHEST*, 2001, 119, 132S-175S (“Geerts”; copy attached to the non-entered amendment filed April 19, 2007) states:

In the summary tables, the rates of deep vein thrombosis have been pooled from the eligible trials for each intervention and then compared with the rate among pooled, untreated or placebo-treated control patients to determine the *reduction in relative risk*. Because comparisons among the interventions are indirect, the results of this pooling analysis provide an approximate guide to the relative efficacy of various prophylactic strategies.

Geerts, at 132S, left-hand column (emphasis added). Thus, a person of ordinary skill in the art would have understood prevention or prophylaxis of a disorder to mean reduction in risk of affliction by the disorder.

Importantly, T.M. Hyers *et al.*, “Antithrombotic therapy for Venous Thromboembolic Disease,” *CHEST*, 2001, 119, 176S-193S (“Hyers”; copy attached to the non-entered amendment filed April 19, 2007) recites:

All antithrombotic therapy with either anticoagulants or platelet-active drugs is prophylactic, since these agents *interrupt progression* of the thrombotic process

Hyers, at 176S, left-hand column. Thus, in yet another sense, a person of ordinary skill in the art would have understood that a treatment that interferes with the progression of a process that leads to a disorder, to be prevention or prophylaxis of that disorder.

Moreover, C.W. Francis *et al.*, “Comparison of Ximelagatran with Warfarin for the Prevention of Venous Thromboembolism after Total Knee Replacement,” *New Engl. J. Med.* 349: 1703 (2003) (“Francis”; copy attached to the non-entered amendment filed April 19, 2007) discusses “prevention” and “prophylaxis” in the same context. Francis at page 1704, second paragraph. Francis also discusses prevention in the same context as risk reduction. Francis at page 1710, first paragraph.

Furthermore, B.I. Eriksson *et al.*, “A Comparison Of Recombinant Hirudin With A Low-Molecular-Weight Heparin To Prevent Thromboembolic Complications After Total Hip Replacement,” *New Engl. J. Med.* 337: 1329 (2003) (“Eriksson”; copy attached to the non-entered amendment filed April 19, 2007) discusses “prevention” in the same context as risk reduction.

In accordance with *Phillips*, it is the contemporaneous understanding of a person of ordinary skill in the art such as that provided above, rather than non-contextual definitions from a general purpose dictionary, that governs claim construction. As indicated in the art discussed above, one of ordinary skill in the art would have

understood that the direct thrombin inhibitors of the claimed invention would therefore be useful for both treating and preventing thrombosis.

D. Request For Entry Of The Proposed Amendment

However, without acceding to the rejection, and solely in an attempt to facilitate prosecution, Applicants propose to amend claims 25, 47, 57 and 116 to delete the phrase "or preventing." It is believed that the "treating thrombosis" language in those claims is consistent with what the Examiner explained at page 3 of the Office Action would be agreeable.

Applicants respectfully request that this amendment be entered, and that this rejection be reconsidered and withdrawn.

IV. The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-120 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Claeson (*Biochem J.*, 1993) in view of Skordalakes (*J. Am. Chem. Soc.*, 1997), and further in view of Kettner (WO 94/21668), Wienand (WO 97/05161) and /or Shoichet (WO 00/35904).

Applicants respectfully traverse this rejection.

A. A Prima Facie Case Of Obviousness Has Not Been Established.

To establish a *prima facie* case of obviousness, the prior art must teach or suggest each and every element of the claimed invention. Additionally, there must be some suggestion or motivation, either in the prior art itself or in the knowledge generally

available to one of ordinary skill in the art, to modify the prior art or combine the teachings of the prior art in the matter posited by the Examiner. *See In re Kahn*, 441 F.3d 977, 987-88 (Fed. Cir. 2006); *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000); and MPEP 2142.

Here, a *prima facie* case of obviousness has not been established. First, even in combination, the cited art would not have suggested a parenteral formulation of a base addition salt of a boronic acid of formula (I) that binds to thrombin. Second, one of ordinary skill in the art would not have had reasonable expectation of success, because he or she would have been led away from the claimed invention.

1. The Prior Art Would Not Have Suggested The Claimed Invention

Briefly, the Examiner asserts (1) that Claeson teaches an organoboronic acid pinanediol ester inhibitor of thrombin having a neutral thrombin S1-binding moiety linked to a hydrophobic thrombin S2/S3-binding moiety; (2) that Skordalakes teaches that the removal of pinacol ester would not alter the analogous thrombin-inhibiting activity of the organoboronic acid; (3) that Kettner demonstrates the “routine knowledge” in removing pinacol ester protecting groups by transesterification to make the boronic ester; (4) that Wienand demonstrates the “routine knowledge” in preparing boronic acid derivatives of formula (I) into various pharmaceutical dosage forms and salt forms; and (5) that Shoichet demonstrates the “routine knowledge” in preparing boronic acid derivatives in various salt forms.

The Examiner asserts that one of ordinary skill in the art would expect that removing the pinacol ester from the compound allegedly disclosed in Claeson would

produce a compound with analogous properties. Office Action at page 9. The Examiner further asserts that preparation of boronic acid derivatives into parenteral dosage forms is well within the skill of the artisan. Office Action at page 10.

Applicants strongly disagree. One of ordinary skill in the art would have had no motivation to make a parenteral formulation of a base addition salt of a boronic acid. Indeed, the Examiner has employed hindsight to analyze whether the claimed invention would have been obvious. However, a hindsight analysis is improper.

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2D (BNA) at 1617. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one “to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher.” *Id.* (quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. (BNA) 303, 313 (Fed. Cir. 1983)).

Kotzab, 217 F.3d at 1369.

Relying, improperly, on a hindsight analysis, the Examiner stated that “Wienand [] makes obvious that the parenteral or intravenous dosage formulation of boronic acid derivatives by the formula I or its salt is *within the skill of the artisan.*” Office Action at page 14 (emphasis added). However, such an approach is improper. Indeed, the MPEP *specifically rejects* the Examiner’s rationale for making this rejection. “The fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish a *prima facie* case of obviousness.” MPEP § 2143.01,

Part IV.

At any rate, this rejection is improper, because even in combination, the cited art would not have suggested a parenteral formulation of a base addition salt of a boronic acid of formula (I) that binds to thrombin, for the following reasons.

The organoboronic molecule disclosed in Claeson is an acid pinanediol ester, not a base addition salt of a boronic acid of formula (I). Moreover, Claeson does not discuss a parenteral formulation. The remaining documents cited by the Examiner fail to cure the deficiencies of Claeson.

Skordalakes relates to X-Ray crystallographic studies of organoboronic free acids that complex with thrombin, not a base addition salt, and not a parenteral formulation.

Kettner discloses merely that an ester protecting group can be removed from a boronic acid. Kettner fails to suggest that a base addition salt of a boronic acid of formula (I) would be suitable for parenteral formulation.

The organoboronic acid disclosed in Wienand is different from the boronic acid of formula (I) of the present application. For example, in claim 1 of the present application, in formula (I), R⁹ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5, or 6 or R⁹ is -(CH₂)_m-W where m is 2, 3, 4, or 5 and W is -OH or halogen. In Wienand, the moiety at what would correspond to R⁹ in formula (I) of the present invention is -(CH₂)₄-NH-CHO, which is a structure that would not have suggested R⁹ in formula (I) of the present invention. Thus, the generic discussion of salts and parenteral administration in Wienand would not have suggested to one of ordinary skill in the art that a base addition salt of a boronic acid of formula (I) of the present invention would be suitable for a parenteral formulation.

Shoichet relates to an organoboronic molecules that are said to be β -lactamase inhibitors, *i.e.*, antibiotics, not thrombin inhibitors. In addition, the structure of the β -lactamase inhibitors in Shoichet are completely different from the structure of the boronic acid of formula (I) of the present invention: the compounds of Shoichet are arylboronic acids (the boronyl group is directly substituted on an aromatic ring), and the skilled chemist would not look to a document containing teaching on aromatic compounds for guidance as to the chemistry of non-aromatic boronic acids (where the boronyl group is not substituted on an aromatic ring), as in the case of the present invention. Thus, the generic discussion of salts and parenteral administration in Shoichet would not have suggested to one of ordinary skill in the art that a base addition salt of a boronic acid of formula (I) of the present invention would be suitable for a parenteral formulation.

It is noteworthy that none of Claeson, Kettner, Skordalakes, Wienand and Shoichet describes the actual preparation of a parenteral or other pharmaceutical formulation. The formulation of drug compounds is a complex subject in its own right and the skilled person seeking to formulate a drug compound would study documents concerned with the formulation of compounds of a similar type to that of the compound in issue. The present invention is concerned with formulating peptide boronic acids and addresses the shortcomings of the prior art by formulating the recited boronic acids as parenteral formulations comprising base addition salts of the acids.

None of Claeson, Kettner, Skordalakes, Wienand and Shoichet represents a starting point for the skilled person looking to provide parenteral formulations of boronic acids – since none of the citations is concerned with formulating boronic acids – and

instead the skilled person would look to the literature concerning formulation of boronic acids and more specifically peptide boronic acids, as discussed in the next section of this reply.

2. *There Was No Reasonable Expectation Of Success, Because One Of Ordinary Skill In The Art Would Have Been Led Away From The Claimed Invention*

The prior art also fail to provide a reasonable expectation of success, which is necessary in order to establish a *prima facie* case of obviousness. MPEP § 2143.02

a. *Boronic Acids Were Known To Be Unstable*

One of ordinary skill in the art would have been *led away* from making a parenteral formulation of a base addition salt of a boronic acid, because boronic acids are known to be unstable. For example, Gupta *et al.*, WO 02/059130 (“Gupta”; of record in the present application), discloses that alkylboronic acids are relatively difficult to obtain in analytically pure form, that they readily form boroxines (anhydrides) under dehydrating conditions, and that they are often air-sensitive, *e.g.*, to oxidation; and concludes that “[t]hese difficulties limit the pharmaceutical utility of boronic acid compounds.” Gupta, at paragraph [0004]. Similarly, S. Wu *et al.*, *J. Pharm. Sci.*, 2000, 89, 758-65 (“Wu”; of record in the present application), reports, “[t]he chemical stability of peptide boronic acid derivatives, from a formulation perspective, has not been extensively reported in the literature to our knowledge. During an effort to formulate 2-Pyz-(CO)-Phe-Leu-B(OH)₂ for parenteral administration, the compound showed erratic stability behavior and was quite unstable in certain solvents.” Wu, at 758, right-

hand column. *See also* the present Specification, at page 4, line 28 to page 5, line 6 (paragraphs [0035] – [0038]).

Aware of the instability of boronic acids and the resultant difficulties associated with making a parenteral formulation of a peptide boronic acid during, a person of ordinary skill, upon reading the references, would have been led in a direction away from a parenteral formulation comprising a base addition salt of a boronic acid.

Indeed, recognizing the “need in the art for improved formulations of boronic acid compounds,” Gupta did not make a base addition salt, but instead explains that that “lyophilization of an aqueous mixture comprising a boronic compound and a compound having at least two hydroxyl groups produces a stable composition that readily releases the boronic acid compound upon dissolution in aqueous media.” Gupta, at paragraph [0006]. In other words, Gupta discloses solving the stability problem by formulating the boronic acid as a lyophilizate. Gupta, at paragraphs [101] and [144].

In a similar vein, V. Martichonok and J.B. Jones, *J. Am. Chem. Soc.*, 1996, 118, 950-58 (“Martichonok”; of record in the present application), discloses formation of the corresponding diethanolamine ester to impart stability to boronic acids. Martichonok, at 951, right-hand column (“[t]his derivatization also provided protection against possible autoxidation of the acetamido boronic acids [] by atmospheric oxygen”). D.S. Matteson *et al.*, U.S. Patent No. 5,681,978 (“Matteson”; of record in the present application), similarly discloses oxidative resistance of the pinacol ester of a boronic acid. Matteson, at column 4, lines 57-67. *See also* the present Specification, at page 4, lines 33-37 (paragraph [0036]).

Thus, aware of both the problem with stability of boronic acids, and two reported solutions to the problem, a person of ordinary skill in the art would not have been motivated to make a parenteral formulation comprising a base addition salt of a boronic acid. Evidence of this is the drug bortezomib (Velcade®), for which the free acid was the subject of Wu and Gupta, and which is marketed as a *mannitol ester*. See the package insert for Velcade® (copy attached to the non-entered amendment filed April 19, 2007) at page 1, lines 10-12. If the claimed parenteral formulation containing a base addition salt of a boronic acid were obvious, why is Velcade® marketed as an ester, and not a base addition salt?

Moreover, the data in Example 34 of the Specification shows that base addition salts of Tri50C are more stable than the free acid.

Further evidence of the nonobviousness of the claimed invention is found in U.S. Patent No. 7,112,572 (copy attached to the non-entered amendment filed April 19, 2007), in Example 13, at columns 50-53, which shows that when incorporated into an enteric-coated hard gelatin capsule, the calcium salt of Tri50c is more stable than the free acid.

Additional evidence of the nonobviousness of the claimed invention is found in the Trigen Ltd. Stability Report (attached to the non-entered amendment filed April 19, 2007) for the free boronic acid TRI-50c (TRI-50c is the boronic acid identified in the present Specification at page 9, line 35 (paragraph [0072])). At page 11 of the stability report, it is shown in Tables 7.1 – 7.3 that if TRI50c is stored for 3 months at 25°C/60%RH, it turns brown (Table 7.1), the moisture content nearly doubles (Table 7.2), and the TRI50c concentration decreases from 97.18% to 58.83% (Table 7.3, line 3).

B. Conclusion

These materials confirm what one of ordinary skill in the art would have known – that free boronic acids are unstable. Armed with that knowledge, one of ordinary skill in the art would not have been motivated to take the organoboronic acid pinanediol ester of Claeson, form the free boronic acid, and formulate the base addition salt.

A *prima facie* case of obviousness has not been established. Applicants respectfully request that this rejection be reconsidered and withdrawn.

V. The Obviousness-Type Double Patenting Rejections Should Be Withdrawn

Claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-116 were rejected, as allegedly obvious over claims 1-38 of Application No. 10/659,179, which has issued as U.S. Patent No. 7,112,572, and over copending Application No. 10/659,178. On April 19, 2007, a terminal disclaimer over U.S. Patent No. 7,112,572, and a terminal disclaimer over copending Application No. 10/659,178 were filed. In the Advisory Action, the Examiner explained that the terminal disclaimers overcame these rejections. Applicants thank the Examiner for withdrawing these rejections.

Claims 1-24, 28-29, 40-46, 58-65, 67-70, 72-78, 81-95, 98-103, 105, 110, 114 and 115 stand rejected for obviousness-type double patenting over claims 19-23 and 28-36 of copending Application No. 10/937,181, and over claims 1-24 and 55-58 of copending Application No. 10/937,854. Applicants respectfully request withdrawal of these rejections, because Application Nos. 10/937,181 and 10/937,854 were each filed September 8, 2004, nearly one year after the filing date of the present application. It is believed that the proposed amendments, evidence and arguments herein place the present

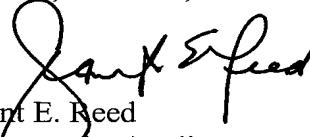
application in condition for allowance. Thus, in accordance with MPEP § 804, it is proper for the Examiner to withdraw the provisional obviousness-type double patenting rejections over Application Nos. 10/937,181 and 10/937,854, and evaluate whether it would be appropriate to require a terminal disclaimer in those later-filed applications.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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